Title: Relation of Dopamine Receptor 2 Binding to Pain Perception in Female Fibromyalgia Patients with and without Depression – an [^{11}C] raclopride PET-study

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Abstract

Dopamine D2/D3 receptor availability at rest and its association with individual pain perception was investigated using the [^{11}C] raclopride PET-method in 24 female Fibromyalgia (FMS) participants with (FMS+, N=11) and without (FMS-, N=13) comorbid depression and in 17 healthy women. Thermal pain thresholds (TPT) and pain responses were assessed outside the scanner. We compared the discriminative capacity, i.e. the individual's capacity to discriminate between lower and higher pain intensities and the response criterion, i.e. the subject's tendency to report pain during noxious stimulation due to psychological factors. [^{11}C] raclopride binding potential (BP), defined as the ratio of specifically bound to non-displaceable radioligand at equilibrium (BP_{ND}) was used as measure of D2/D3 receptor availability. We found significant group effects of BP_{ND} in striatal regions (left ventral striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS- compared to healthy subjects. Correlational analysis showed negative associations between TPT and D2/D3 receptor availability in the left caudate nucleus in FMS-, between TPT and D2/D3 receptor availability in the right caudate nucleus in FMS + and positive associations between TPT and D2/D3 receptor availability in the left putamen and right caudate nucleus in healthy controls. The response criterion was positively associated with D2/D3 receptor availability in the right nucleus accumbens in FMS – and negatively with D2/D3 receptor availability in the left caudate nucleus in healthy controls. Finally, no significant associations between D2/D3 receptor availability and discriminative capacity in any of the groups or regions was determined. These findings provide further support for a disruption of dopaminergic neurotransmission in FMS and implicate DA as important neurochemical moderator of differences in pain perception in FMS patients with and without co-morbid depression.

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Introduction

Fibromyalgia syndrome (FMS) is an idiopathic, diffuse soft-tissue pain syndrome with unclear pathophysiology (Wolfe, 1990). Major depressive disorder (MDD) is the most frequent psychiatric comorbidity in FMS (Fietta, Fietta, & Manganelli, 2007). A growing awareness of the role of mesolimbic dopamine (DA) in pain perception, specifically in anti-nociception, has emerged in recent years (Hagelberg et al., 2004; Jarcho, Mayer, Jiang, Feier, & London, 2012; Wood, 2008). Although its precise function in nociceptive processes is only partially understood, DA regulation has been shown to be disrupted in MDD and chronic pain (Epstein et al., 2006; Wood, 2008). Several Positron Emission Tomography (PET)- studies demonstrated altered post-synaptic striatal DA neurotransmission in chronic neuropathic pain syndromes including burning mouth, and atypical facial pain, (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003; Wood, Schweinhardt, et al., 2007) while an alteration of presynaptic DA transmission was evidenced in FMS (Wood, Patterson, et al., 2007). Results of *in vivo* DA studies in MDD brought contradictory results (recently reviewed by (Savitz & Drevets, 2013)). When differences were found they indicated a reduced DA function in MDD that was however influenced by medication. However, postsynpatic DA function has not been investigated so far in FMS and the role of depression in the DA changes observed in chronic pain is not clear.

Moreover a positive correlation between individual pain sensitivity and striatal baseline raclopride binding was observed in healthy volunteers (Hagelberg et al., 2002; Pertovaara et al., 2004; Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006). Pain sensitivity can be determined using the Signal Detection Theory (SDT) that distinguishes two measures: the discriminative capacity, a measure of neurosensory sensitivity, reflecting the subject's ability to discriminate between two stimuli of similar, yet distinct, intensities. A low discriminative capacity is associated with relative insensitivity to noxious stimulation and indicates an attenuation of neural activity in the sensory system (Clark & Mehl, 1971). The response criterion is independent from discriminability and locates the person's overall tendency to report pain; a high value indicates a stoical attitude (Clark & Mehl, 1971). The response criterion and thermal pain threshold (TPT) were shown to be inversely correlated with the D2/D3 Binding Potential (BP) in the right putamen in healthy volunteers, whereas the sensory

discriminative capacity was not significantly correlated with the D2/D3 BP in any striatal region (Pertovaara et al., 2004). The association between measures of pain sensitivity with D2/D3 binding has not been yet examined in chronic pain conditions.

Here, we investigated the D2/D3 receptor availability at rest between FMS participants with (FMS+) and without (FMS –) comorbid depression compared to healthy controls using the [^{11}C] raclopride PET method to measure postsynaptic striatal D2/D3 receptor availability. We expected FMS patients to show reduced [^{11}C] raclopride binding (measures as the ratio of specifically bound to non-displaceable radioligand at equilibrium (BP_{ND}) in striatal regions compared to healthy controls, reflecting a decreased postsynaptic availability of D2/D3 receptors in these patients as already described at the presynaptic levels (Wood, Patterson, et al., 2007) and in agreement with findings for neuropathic pain conditions (Hagelberg, Forssell, Aalto, et al., 2003; Hagelberg, Forssell, Rinne, et al., 2003). We expected the reduction to be more pronounced in FMS+ patients than FMS- patients. Additionally, we aimed to test the association between pain sensitivity and striatal D2/D3 receptor availability with regard to the role of comorbid MDD. We expected FMS patients to have decreased thermal pain thresholds (TPT) and thermal pain tolerance (TOL), correlated to altered D2/D3 receptor availability, but for pain responses to show no correlation with BP_{ND} in striatal regions. Together, we believe that such evidence would indicate that the dopaminergic influence on pain sensitivity is impaired in FMS.

Experimental procedures

Subjects

Given the predominance of women in FMS (Wolfe, Ross, Anderson, Russell, & Hebert, 1995) and to reduce the heterogeneity of study samples, we decided to only include women in this study. A total of 24 female FMS patients were compared to 17 age- and gender-matched healthy control subjects. Among the FMS patients 11 subjects were diagnosed with comorbid MDD. All FMS+ patients had the onset of MDD subsequent to the FMS diagnosis. A description of clinical and demographic data parameters for the FMS patients is provided in Table 1. FMS patients fulfilling the American College of Rheumatology (ACR) classification criteria for Fibromyalgia (Wolfe et al., 1990) with decreased

pressure pain thresholds at a minimum of 11 of 18 specific tender points, located in 9 paired regions of the body, were recruited from the Division of Rheumatology at the University Hospital Zurich. They were recruited through flyers in medical practices, advertisements in newspapers, and advertisements on websites associated with FMS. Controls were recruited through flyers on bulletin boards in public places. Current and/or chronic medical conditions, current and/or lifetime psychiatric diagnoses, acute or chronic pain and medication other than oral contraceptives were exclusion criteria for the controls. All FMS patients had their FMS diagnosis confirmed by an experienced rheumatologist (HS) through clinical examination, including measurements of pain thresholds at tender points using a digital dolorimeter (LD 100 NRS, AC Engineering Basel, Switzerland). FMS subjects had a mean pain duration of 13.46 years (SD=11.98), and a mean number of 16 tender points (SD=3.66). FMS subjects were allowed to continue their SSRI (selective serotonin-reuptake inhibitors), TCA (tricyclic antidepressants) and NSAID (non-steroidal anti-inflammatory drugs) medication during the study. A total number of 12 FMS patients were taking antidepressant medication either for pain or depressive symptoms. The use of opioids, neuroleptics, antiepileptics, and lithium was an exclusion criterion. All subjects were tested for comorbid psychiatric disorders using the SCID (Structured Clinical Interview for DSM-IV (First, 2002)). This instrument was also used to diagnose MDD in the FMS group. The severity of depression was measured with the Beck Depression Inventory (BDI) , German version (Hautzinger, Bailer, Worall, & Keller, 1995), and the Montgomery Åsberg Depression Scale (MADRS) (Montgomery & Asberg, 1979). Anxiety was assessed using the State-Trait Anxiety Inventory (STAI) (Laux, Glanzmann, Schaffner, & Spielberger, 1981). All participants were screened for general MRI and PET exclusion criteria, pregnancy (pregnancy test on the day of scanning), and breast-feeding. They were required to sign an informed consent which explained the procedures of the study prior to information and testing. The study was approved by the Ethical Committee of the Canton Zurich and the Swiss Federal Department of Health in accordance with the current version of the declaration of Helsinki and the Swiss regulatory requirements.

PET image acquisition

[^{11}C] raclopride is an established *in vivo* method for estimating the availability of D2/D3 receptors in the brain. The D2/D3 receptor antagonist [^{11}C] raclopride was produced on site according to Good Manufacturing Practice (GMP) guidelines. PET scans were acquired using a PET/CT scanner with an axial field of view of 15.3 cm in 3D mode (Discovery STE, GE Healthcare, Waukesha, WI, USA) at the Department of Nuclear Medicine at the University Hospital Zurich. PET data were reconstructed using filtered back projectioned segmented attenuation correction, for which a low dose CT scan was acquired.

On the day of the PET study, subjects were asked to eat a well-balanced meal before the PET scanning and not to consume too many liquids to ensure personal comfort during the scans. The PET measurement took place in the same time frame (Monday afternoon from 3 pm to 5pm) for all participants. [^{11}C] raclopride was injected as a slow bolus (260+/-20 MBq). Mean specific activity of the tracer at time point of injection was (M=121.75GBq/µmol, SD=43.63). Dynamic scanning was initiated at the time of tracer injection and continued for 60 min (31 frames of 4x15sec, 8x30sec, 9x60sec, 2x180sec, 8x300sec, total 60 min duration). Image data from 40-50 minutes were averaged and exported for further processing in the PMOD software (Version 3.2, PMOD Technologies, Zurich, Switzerland).

Magnetic resonance imaging

Each subject received a high-resolution T1 weighted magnetic resonance scan (3D fast-field echo scans with 160 slices, 1mm isotropic resolution, TR= 18ms, TE= 10ms, flip angle= 30°) on a Philips Ingenia Scanner for co-registration with PET images. All images were checked for structural abnormalities and lesions by a clinical neuroradiologist.

Determination of thermal pain threshold (TPT), pain tolerance threshold (TOL), and pain modulation

Standardized pain testing procedures were conducted by the same investigator on the same day as the PET scanning with each subject in a separate session in a quiet room with constant ambient temperature. Thermal pain threshold (TPT) and thermal pain tolerance (TOL) were determined using a

method of limits procedure (Hansen, Hopf, & Treede, 1996). Thermal cutaneous pain response was measured by delivering heat stimuli to the thenar of the non-dominant hand with a 27-mm-diameter thermal contact thermode (CHEPS, Medoc Ltd, Ramat Yishai, Israel). The CHEPS thermode has a heating rate of 70°C/s and a cooling rate of 40°C/s. The same heating and cooling rate was applied during the whole procedure. The CHEPS thermode has a subject response device that immediately records the temperature once activated, and resets the thermode to the adaptation temperature in preparation for the next trial. The area of the stimulus surface was 5.7. cm^2. TPT and TOL estimation was based on five thermal stimuli starting at 32°C and rising linearly at a rate of 1°C/s until it was stopped either by a button press or when the maximum temperature of 52°C was reached. To determine TPT, subjects were asked to press the button on the response device when they experienced pain for the first time. To examine TOL, subjects were asked to push the response button when the sensation on their hand became intolerable or unbearable. The experimental paradigm for the pain modulation was adapted and slightly modified from the study of (Pertovaara et al., 2004). Heat stimulation started at 34.5°C and the temperature was increased linearly at a rate of 3°C/s to one of the six predetermined temperatures (45.8, 46.3, 46.8, 47.3, 47.8, and 48.3°C) for a duration of 4s, after which the stimulus temperature returned to baseline. The interval between successive stimulations was 15s. Each stimulus temperature was applied eight times and the order the stimuli were presented was randomized across subjects. After presentation of each stimulus, the subject was asked to rate the sensation evoked by the stimulus using a numerical rating scale ranging from 0 = no pain at all to 10 = strongest pain imaginable. Before the actual testing sessions all subjects went through a brief training session in which they were introduced to the experimental condition. The area of stimulation was slightly varied by moving the thermode either to the left or right side for each trial to prevent sensitization.

Determination of the subject's discriminative capacity and response criterion

We chose the same components as (Pertovaara et al., 2004) derived from the Signal Detection Theory (SDT) to determine the individual response characteristics to pain. Discriminative Capacity was computed by the trapezoidal rule as the area below the Receiver Operating Characteristics (ROC)

Curve which is generated by cumulating probabilities of hits and false alarms for each response elicited by the stimulus temperatures of 46.8° vs. 47.3° using PASW Statistics 21.0 (SPSS Inc., Chicago, Ill, USA). The exact description of the calculations of the response criterion is provided in detail elsewhere (Pertovaara et al., 2004). Briefly, the criterion was defined as the rating scale criterion where half the responses (to both stimulus intensities in each pair) are divided into higher response categories and the other half into lower response categories. The response criterion was defined as $C=0.5(Z_{SN}+Z_N)$. Within the calculation, the probability of rating a stimulus of 47.3° as painful (rating categories 6-10 pooled together) was converted to a Z score (Z_{SN}) as described by Gescheider (1997, pp.122-123 and Table A). The probability of rating a stimulus of 46.8° as non-painful (rating categories 1-5 pooled together) was also converted to a Z score (Z_N).

Data analysis

ROI analysis

All PET emission scans were reconstructed using 3D filtered back projection including a 6mm FWHM Hanning filter, producing an estimated final FWHM (full width at half maximum) of 10-12mm. Corrections for subject motion during the 60 min PET acquisition were performed with a mutual information registration of each image frame to a standard frame (0-8min after injection) before attenuation correction. Based on the calculated motion, the transmission images were re-sliced and projected for final attenuation correction, reconstruction and realignment. The realigned frames were summed to generate an image that was co-registered with the corresponding MRI image using PMOD software Version 3.2 (PMOD Technologies Ltd, Zurich, Switzerland). This was performed for the first 8 minutes of scanning, during which the radiotracer distribution was most sensitive to cerebral blood flow (CBF), and thus for the cortical outlines to be sufficiently evident in order to guide image co-registration. The PET frames were summed and co-registered with the corresponding magnetic resonance image, and both images were transformed linearly into standardized stereotaxic space using the Montreal Neurological Institute template. Mean tissue radioactivity concentrations were extracted using MRI based regions of interest (ROI's), defined on a template MRI image using PMOD software in the anteroventral striatum, putamen, nucleus accumbens, caudate nucleus and cerebellum after

Drevets et al. (Drevets et al., 2001). Each individual MRI was registered to the template brain and the ROI's were repositioned as needed to accommodate for individual differences in anatomy. The anatomical accuracy and symmetry of each set of individual ROI's was verified by a neuroscientist familiar with striatal anatomy (CMS). These ROI's were then back-transformed into the subject's native MRI space and applied to the co-registered PET images (example in Figure 1). Simplified reference tissue model (SRTM) (Lammertsma & Hume, 1996) was used for derivation of binding potential (BP) using the cerebellum as reference region. The outcome measure was binding potential, defined as the ratio of specifically bound to non-displaceable radioligand at equilibrium (BP_{ND}) . BP_{ND} can also be described as $BP_{ND} = f_{ND} * (B_{max}/K_D)$ where Bmax is the concentration of D2/3 receptors, K_D is the inverse of the affinity of the radiotracer for the receptor, and f_{ND} is the free fraction in the nonspecific distribution volume of the brain. For each region, the BP_{ND} for patients and controls were compared with those for FMS+ and FMS- patients and controls. Relationships between BP_{ND} and the pain thresholds and measures were analyzed with the Pearson product-moment correlation coefficient. A two-tailed probability value of $p<0.05$ was chosen as the level of significance. Since age is known to affect D2/D3 receptor BP, this factor was included in the analysis.

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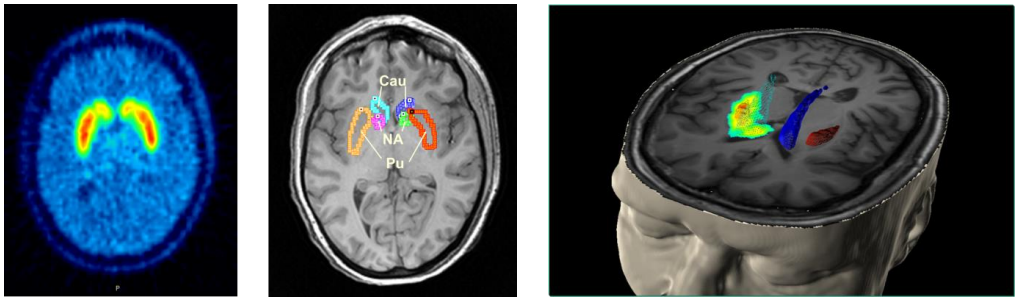

Figure 1: ROI's placement. Transverse view Cau: Nucleus caudatus; NA: Nucleus accumbens; Pu: Putamen

Analysis of behavioral data

PASW Statistics 21.0 software (SPSS Inc., Chicago, Ill, USA) was used for statistical analysis. Data distribution was tested with the Kolmogorov-Smirnov test and by observing data histograms. The results of normally distributed data are presented as mean +/- standard deviations. One way analysis of

variance (ANOVA) was used to assess differences in D2/D3 receptor availability between groups (healthy, FMS-, FMS+) for each region of interest. Since age is known to affect D2/D3 receptor BP, this factor was included in the analysis. Additional analyses included FMS duration, antidepressant medication and BDI as factors. The difference between groups for experimental pain ratings (pain threshold, discriminative capacity, and response criterion) of each group was tested using independent samples t-tests and one-way ANOVA followed by post-hoc tests, where appropriate. $P<0.05$ was considered to represent a statistically significant difference.

Associations between D2/D3 receptor availability and psychophysical results (pain threshold, discriminative capacity, response criterion) were determined using Pearson's coefficient of correlation. $P<0.05$ was considered as statistically significant.

Results

ROI Analyses

Mean BP_{ND} are summarized in Table 2. Analysis of postsynaptic D2/D3 receptor availability, measured by [^{11}C] raclopride, demonstrated a significant group effects between healthy subjects, FMS- and FMS+ patients in the left ventral striatum (F(2.33)=5.3, p=0.01), left caudate nucleus (F(2.33)= 3.8, p=0.03), and the left nucleus accumbens (F(2.33)= 4.1, p=0.03) after controlling for the effect of age (see Table 3). The covariate age was significantly related to the BP_{ND} in the left ventral striatum (F(1.33)=19.9, p=0.01). Simple contrasts revealed significantly less BP_{ND} in the left caudate nucleus and left nucleus accumbens in FMS+ patients compared to healthy controls (p=0.01, resp. p=0.02) and significantly less BP_{ND} in the left ventral striatum in FMS- than FMS+ patients (p=0.02). In additional analyses with the covariates BDI, FMS duration and antidepressant medication no significant correlations were found with BP_{ND} in any striatal regions (p>0.1).

Experimental pain ratings (TPT, TOL, response criterion, discriminative capacity)

Table 3 represents the mean values of all experimental pain ratings.

An independent samples t-test was conducted to compare TPT and TOL between all FMS patients (n=24) and healthy controls (n=17). FMS patients showed a significantly lower TPT (m=41.1, SD=4.5) compared to healthy subjects (m=45.0, SD=4.4; $t(39)=2.8$, $p=0.01$). Also the TOL was significantly lower in FMS patients (m=44.7, SD=3.7) compared to healthy subjects (m=47.7, SD=3.7; $t(39)=2.5$, $p=0.02$). One-way ANOVA considering 3 groups of subjects showed significant effects for TPT ($F(2,38)=4.34$, $p=0.02$) and TOL ($F(2,38)=3.7$, $p=0.03$). A post-hoc Gabriel test indicated that FMS+ patients reported a significantly lower TPT ($p<0.02$) and TOL ($p<0.03$) than healthy subjects. The FMS- group did not significantly differ from the other two groups. The index of response bias (response criterion) and the discriminative capacity did not differ significantly between the three groups ($F(2.35)=0.61$, $p>0.94$, resp. $F(2.16)=1.18$, $p>0.33$ for discriminative capacity). The response criterion was not significantly correlated with TPT (healthy subjects $p>0.6$, FMS- $p>0.07$ and FMS+ $p>0.9$) or TOL (healthy subjects $p>0.3$, FMS- $p>0.3$, FMS+ $p>0.09$). Discriminative capacity was not associated with TPT (healthy subjects $p>0.3$, FMS- $p>0.4$, FMS+ $p>0.2$) or TOL (healthy subjects

289 p>0.4, FMS- p>0.7, FMS+ p>0.2) in any of the groups. FMS duration, antidepressant medication or
290 BDI were not significantly correlated to TOL or TPT (p>0.1).
291
292 **Correlation of D2/D3 receptor availability with pain responses**
293 *Thermal Pain Threshold (TPT)*
294 In FMS+ patients, striatal D2/D3 receptor availability in the right nucleus caudate was significantly
295 correlated with TPT (r= 0.65, p=0.03) (see Figure 2). In FMS- patients, striatal D2/D3 receptor
296 availability in the left caudate nucleus was significantly correlated with TPT (r=0.66, p=0.02), (see
297 Figure 3).
298 In healthy subjects, striatal D2/D3 receptor availability in the left putamen (r=0.56, p=0.01) and right
299 caudate nucleus (r=0.513, p=0.05) were significantly associated with TPT (see Figure 4).
300
301 *Thermal Pain Tolerance (TOL)*
302 No significant correlations between striatal D2/D3 receptor availability and TOL were found in any of
303 the three groups (p>0.2).
304
305 *Response criterion*
306 Healthy subjects showed a significant correlation of the response criterion with the D2/D3 receptor
307 availability in the left caudate nucleus (r=-0.645, p=0.001) (see Figure 5). FMS– showed a significant
308 correlation of the response criterion with the D2/D3 receptor availability in the right nucleus
309 accumbens (r=0.67, p=0.03) (see Figure 6). No significant correlations of the response criterion with
310 the D2/D3 receptor availability in any striatal region could be determined for FMS+.
311
312 *Discriminative capacity*
313 The index of the subject's discriminative capacity, the area under the ROC curve, varied over a wide
314 range between the subjects and did not differ significantly between the three groups (F(1.38)=2.1,
315 p=0.15). Correlations of the discriminative capacity with the D2 receptor availability were not
316 significant (p>0.17) in any of the three groups.
317

Discussion

The major innovation of the present study was that it examined the link between striatal D2/D3 receptor availability and individual pain perception in FMS patients, both with and without comorbid MDD, compared to healthy subjects using the [^{11}C] raclopride PET method. To our knowledge, this is the first study investigating the link between striatal D2/D3 receptor availability and individual pain responses in FMS that differentiated between individuals with and without depression.

In line with our expectations, we found significant group differences in BP_{ND} in striatal regions (left ventral striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS- compared to healthy subjects. Furthermore, the correlational analyses showed different associations between striatal D2 receptor availability and thermal pain thresholds that differentiated between FMS patients with and without depression and healthy controls. We found negative associations of D2/D3 receptor availability in the left caudate nucleus in FMS- and right caudate nucleus in FMS+. In healthy subjects, the thermal pain threshold correlated positively with D2/D3 receptor availability in the left putamen and right caudate nucleus. Further, for the response criterion, we found a positive association with D2/D3 receptor availability in the right nucleus accumbens in FMS- patients and a negative correlation of the response criterion with D2/D3 receptor availability in the left caudate nucleus in healthy controls. Finally, no correlations between D2/D3 receptor availability and discriminative capacity in any of the groups or regions could be determined. Taken together, these findings provide further support for a disruption of dopaminergic neurotransmission in FMS and implicate DA as important neurochemical moderator of differences in pain perception in FMS patients with and without co-morbid depression. Our findings are similar to previous studies which have demonstrated reductions in 6-^{18}F fluoro-L-DOPA uptake in dopaminergic centers of the midbrain (i.e. ventral tegmental area and substantia nigra) in FMS (Wood, Patterson, et al., 2007), and lower raclopride BP in FMS patients than healthy controls in all functional sub-regions of the striatum during non-painful saline infusion (Wood, Schweinhardt, et al., 2007). However, it is not entirely clear if this result reflects decreased DA receptor density or a greater release of DA in response to non-painful saline infusion and is therefore not directly comparable to our experimental paradigm. No study so far has investigated the baseline DA changes at the post-synaptic level in Fibromyalgia (i.e. in the absence of

noxious stimuli). Furthermore, several Positron Emission Tomography (PET) studies evidenced an increased D2 receptor availability in chronic neuropathic pain conditions such as burning mouth syndrome (Hagelberg, Forssell, Rinne, et al., 2003) or atypical facial pain (Hagelberg, Forssell, Aalto, et al., 2003) suggesting a contribution of reduced dopaminergic inhibition to the chronic pain condition. Our results indicating the opposite changes suggest that FMS patients differ from neuropathic pain patients at a neurochemical level. Interestingly, we found significantly less BP_{ND} raclopride binding in FMS patients with depression compared to those without depression in the left ventral striatum, a region that has been shown to be associated with emotional processing of pain (Scott et al., 2006). This suggests that FMS patients with and without depression can also be distinguished on a neurochemical level which might also influence treatment options. FMS patients with comorbid depression showed significantly less [^{11}C] raclopride binding in the left caudate nucleus and nucleus accumbens compared to healthy controls, suggesting more free DA receptors or dysfunctional receptors in these patients.

The Sensory Detection Theory analysis showed that Fibromyalgia patients with and without depression did not set a higher criterion for reporting pain and did also not differ in terms of discriminative capacity from our healthy controls. Consistent with previous studies, the thermal pain tolerance and thresholds of the FMS patients in our study differed from healthy controls, further confirming the findings of greater responsiveness to pain in FMS induced by a wide variety of stimulus modalities (Klauenberg et al., 2008). However, we found no difference in terms of thermal pain threshold and tolerance between FMS patients with and without comorbid MDD, which was also described in another study comparing FMS patients with and without comorbid MDD (de Souza, Goffaux, et al., 2009). The results from the correlation analysis between D2/D3 receptor availability and psychophysical results in Fibromyalgia patients with and without depression support a disrupted pain modulatory role of striatal D2 receptors in FMS. Our results suggest a potential link between D2/D3 receptor availability and pain perception due to psychological factors in FMS which differ however between patients with and without comorbid depression. In Fibromyalgia patients without depression, D2/D3 receptor availability in the right nucleus accumbens was positively associated with the criterion to report pain, but not in FMS patients without comorbid depression. Since the response

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criterion is a measure for psychological aspects of pain, the pain sensitivity in Fibromyalgia patients without depression appears to be determined mainly by a dopaminergic influence on psychological factors that in turn influence the subject's tendency to report pain rather than by physiological factors. In line with this finding psychological factors have been shown to have an important role in variability of pain ratings between subjects (Clark & Mehl, 1971). On the other hand cognitive and affective variables frequently occurring in FMS such as depression, anxiety or pain-related anxiety (Lachaine, Beauchemin, & Landry, 2010; Rutledge, Mouttapa, & Wood, 2009) were related to increased pain report and responses. Also personality traits associated with FMS (Malin & Littlejohn, 2012) such as detachment, anxiety, and novelty seeking, were related to D2/D3 receptor availability (Breier et al., 1998; Farde, Gustavsson, & Jonsson, 1997; Suhara et al., 2001) and increased pain report (Farde et al., 1997). This matches the assumption that emotional and psychological processes may play a particularly important role in promoting pain in these patients and that affect may contribute to pain in FMS (Staud, Price, Robinson, & Vierck, 2004). In addition, D2 receptor-mediated neurotransmission in the ventral system involving the nucleus accumbens, has been shown to be associated with emotional processing of pain (Scott et al., 2006). Consistent with the possibility that psychological factors contribute to pain in FMS via DA transmission, it has recently been proposed that DA could play a role in modulating the salience of a pain stimulus (Becker et al., 2013), fostering coping responses, rather than having direct anti-nociceptive effects. This mediating role of DA might eventually explain why we found associations between striatal D2/D3 receptor availability in regions associated with emotional modulation of pain and psychophysical measures of emotional/attitudinal aspects of pain in our FMS patients. In Fibromyalgia patients with depression, D2/D3 receptor availability in the right caudate was negatively associated with thermal pain threshold, but not with the response criterion or discriminative capacity. Evidence showing that D2 receptor-mediated neurotransmission in the dorsal caudate and putamen is associated with subjective ratings of sensory and affective qualities of pain (Scott et al., 2006), suggests that D2/D3 receptor availability in the right caudate of Fibromyalgia patients with depression influences non-sensory mechanisms underlying the pain response rather than actual pain sensitivity. These results are in line with a previous fMRI study which suggested that the presence of depression had no effect on the sensory-discriminative

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processing of pain stimulation but had a selective effect on brain regions that process the affective-motivational dimension of pain (Giesecke et al., 2005). Furthermore, this result and the fact that FMS patients with depression conveyed a lower pain threshold than the other subject groups, support the idea of a more pronounced deficit in pain inhibition in FMS with comorbid depressive symptoms (de Souza, Potvin, Goffaux, Charest, & Marchand, 2009), suggesting that depression could influence pain perception in FMS via DA. Our findings in Fibromyalgia patients with and without depression are not consistent with previous reports in healthy subjects where the pain threshold and the response criterion were inversely correlated with the D2/D3 BP in the human striatum (right putamen) (Pertovaara et al., 2004). The same study showed that the discriminative capacity is not a critical factor responsible for the association of pain responses with D2/D3 BP in healthy subjects (Pertovaara et al., 2004). This result is in line with our findings both in healthy subjects and Fibromyalgia patients. In accordance with our hypothesis, we found significant positive correlations between the thermal pain threshold and D2/D3 receptor availability in striatal regions including the left putamen, and the right caudate nucleus in healthy subjects. This result however, contradicts previous findings that reported direct correlations between striatal D2/D3 receptors and pain thresholds in the right putamen (Hagelberg et al., 2002; Pertovaara et al., 2004). Lateralization differences in the DA system are well documented and an influence of gender on lateralization of the function of the DA system has previously been shown (Martin-Soelch et al., 2011). The deviation from the previous finding could therefore be explained by the inclusion of women in our study while the other studies included only men (Pertovaara et al., 2004). Furthermore, some pain-related phenomena such as pain threshold have been shown to occur with a laterality bias (Lugo, Isturiz, Lara, Garcia, & Eblen-Zaijur, 2002). Moreover, associations between the D2 binding capacity and conditioned pain modulation, which reflects the capacity of the brain to inhibit and to modulate incoming pain signals, have been reported in the left putamen (Hagelberg et al., 2002).

Several previous PET studies also using [^{11}C] raclopride showed increased D2 receptor availability in chronic neuropathic pain conditions such as burning mouth syndrome (Hagelberg, Forssell, Rinne, et al., 2003) or atypical facial pain (Hagelberg, Forssell, Aalto, et al., 2003). An overlapping pathophysiology between FMS and neuropathic pain has been suggested due to shared clinical

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features such as paresthesias, hyperalgesia and allodynia (Maletic & Raison, 2009), but our results indicate that striatal D2/D3 receptor availability in FMS patients with and without depressive symptoms are not impaired in the same way as in chronic neuropathic pain conditions. Abnormal sensory thresholds were also evidenced in neuropathic pain such as burning mouth syndrome or trigeminal non-idiopathic neuropathic pain (de Siqueira, Teixeira, & de Siqueira, 2013). Abnormal sensory findings are considered important features in the classification of neuropathic pain according to the International Association for the study of pain (IASP). Therefore, the observation of abnormal sensory thresholds and the disrupted modulatory role of striatal D2/D3 receptors in pain processing in FMS could be added to other neuronal changes observed in these patients (for instance impaired small fiber function in FMS) (Uceyler et al., 2013), contradicting the opinion that FMS is a pure somatization disorder without demonstrable abnormality.

Some limitations merit attention. This study did not allow for differentiation between D2/D3 receptor density or intrasynaptic dopamine concentration and the interpretation of underlying neuronal factors should be treated with caution. Prior work indicates that [^{11}C] raclopride values from the bolus method are almost identical to binding values generated by a bolus-infusion method (Carson, 2000), in which DA release can be indirectly measured for the same subjects. Although SPM analysis of PET ligand studies is a viable alternative to ROI analysis, especially for the exploration of changes without a priori region definitions, requirements of the analysis include transformation of the PET data to standard anatomical space, smoothing of the data and quantitative normalization to account for global effects. In a small cohort as in our study, these processes may reduce the sensitivity to subtle changes in raclopride binding. Standardization of the basal ganglia anatomy for SPM analysis is a known challenge (in comparison to cortical anatomy). Therefore, our individual anatomy MR-based VOI analysis may be considered to better account for individual basal ganglia anatomy and improve the sensitivity of our PET measurements. Further, we did not correct for multiple comparisons, and therefore it remains possible that our results would not survive methods for the correction of multiple testing. Another limitation is that we did not include chronic neuropathic pain patients to control for similarities or differences between FMS and neuropathic pain. A further limitation is that the painful

stimuli were not adapted to the different pain thresholds of FMS patients and controls thus making the comparison of the evoked processes difficult. Further, we did not control for phases of menstrual cycle in our participants. However, the majority of the participants were postmenopausal (N=19, see Table 1). Finally, DA receptor binding results as well as the individual responses to pain may have been biased by the patients' medication, which possibly influenced the testing procedures, including slower reaction times and anti-nociceptive effects of antidepressants (N=12). Nevertheless, we found significant differences between FMS patients and healthy subjects with regard to the estimation of pain thresholds, and a previous study (Klauenberg et al., 2008) found no significant group difference concerning SSRI medication regarding all pain thresholds. It is however possible that the lack of differences in D2/D3 receptor availability may be related to the medication.

Conclusion

To our knowledge, this is the first report on the association between D2/D3 receptor availability and pain perception in FMS, distinguishing between FMS patients with and without comorbid depression. Additionally, in comparison to previous studies in this field, our study included a relatively large sample of patients. In conclusion, our data suggest that there are differences in D2/D3 receptor availability at rest between FMS patients with depression and without depression compared to healthy subjects. This study presents novel results suggesting that the association between D2/D3 receptor availability and pain perception differs between healthy subjects and patients with Fibromyalgia. Furthermore, this association also differed between FMS patients with and without depression, suggesting that depression could influence pain perception in FMS. Our results suggest that alterations in the dopaminergic system appear to be linked to pain sensitivity in FMS patients. Striatal D2/D3 receptor availability in FMS patients with and without depression is associated with psychological aspects of pain rather than the discriminative capacity of the sensory system mediating pain. However, the exact mechanisms have yet to be elucidated and similarities with chronic neuropathic pain patients with regard to the modulatory function of DA in pain should be further explored. These findings contribute to the understanding of the function of the dopaminergic system in central pain processing in healthy individuals and in patients with FMS.

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Declaration of conflicts of interest:

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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